Smallpox Vaccination is Not Associated with Infertility in A Healthy Young Adult Population

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Report No. 07-27

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140 Sylvester Road
San Diego, California 92106

[Human Vaccines 4:3, 224-228; May/June 2008]; ©2008 Landes Bioscience

Research Paper

Smallpox vaccination is not associated with infertility in a healthy young adult population

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Abbreviations: CI, confidence interval; ICD-9-CM, international classification of diseases, 9th revision, clinical modifications

Key words: infertility, smallpox vaccine, military personnel, reproductive health, vaccination

Concerns exist regarding reproductive health, including potential infertility, among young adults with military-related occupational exposures. This study evaluated infertility diagnoses in a large population of healthy young adults in relation to prior smallpox vaccination. Using a retrospective cohort design, the population consisted of United States military members eligible for smallpox vaccination in 2003–2004 who had electronic health care utilization records available through at least December 2005. Multivariable logistic regression models were applied to evaluate infertility among male and female populations separately. Among 253,973 men and 44,332 women included in these analyses, the adjusted odds of infertility diagnoses in those with prior smallpox vaccination were 0.94 [95% confidence interval (CI), 0.83–1.06] and 1.10 (95% CI, 0.94–1.28), respectively. Therefore, no association was found between smallpox vaccination and subsequent infertility diagnoses in either men or women. This study represents the first large epidemiologic investigation of infertility after the smallpox vaccine.

Fertility, or the ability to conceive and have conception result in live birth, is an important component of reproductive health. In the United States, 3.4 million married men self-report that they or their partner have received fertility services.[1] Male and female factors, alone or in unison, can contribute to infertility, although for over 20% of cases, the cause is unknown.[2] Parental environmental exposures can negatively impact fertility, with some research suggesting effects on ovarian function, semen quality and increased risk of early fetal loss.[3-5] Parental occupation is an important source of exposure to potentially harmful agents, and effects on fertility have been demonstrated in a wide range of occupations, including agricultural workers, lead workers and female workers in the semiconductor industry.[6-9] Military service members encounter a host of unique occupational exposures, some of which may affect several aspects of reproductive health, including fertility.

Deployments to wars and associated military-unique exposures have caused great concern and resource-intensive research to assess the later appearance of birth defects in children.[10-18] To a lesser degree, research has also examined the impact of military-unique exposures on fertility. Limited epidemiologic studies exploring fertility outcomes for veterans of the first Gulf War had mixed results; conclusions were limited because specific exposures among deployers were not defined.[18-22] Other studies focused on certain military occupations have not consistently demonstrated associations between duty assignments and subfertility.[23-25] Exposures differ by service branch, military occupation and duty location, making studies of fertility challenging in these populations.

Immunizations represent one set of exposures that may cause especially heightened concern, including concerns about fertility, among young adults.[22,26] Some military men have opted to cryopreserve semen because of their concerns about deployment-related exposures, including vaccines.[27] There are few studies that explore the effects of infectious disease vaccinations on subsequent fertility. One analysis showed no relationship between prior anthrax vaccination and semen parameters in a population of men who were seeking fertility treatment with their partners.[28] Another study demonstrated that bacille Calmette-Guérin vaccine reduced semen parameters when given in conjunction with chemotherapy in certain cancer patients.[29] Studies of other immunization effects on fertility and reproductive health have been very limited.

In early 2003, the United States instituted a National Smallpox Vaccination Program for early responders and military service members.[30] Wyeth Laboratories produced the approved vaccine, Dryvax®, using a formulation first used in 1931.[31] Prior to the establishment of the smallpox vaccination program, the vaccine had been used worldwide for over half a century when smallpox was still a naturally circulating disease. Because of this, detailed documentation exists of the vaccine's short-term adverse health effects,[31-33] but there are limited data on its impact on reproductive health. Historical data suggest that infants born to women who are inadvertently vaccinated while pregnant do not have increased risk for most adverse outcomes, and a modern registry exists to monitor outcomes among women vaccinated while pregnant.[34-37]

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Submitted: 09/24/07; Revised: 12/14/07; Accepted: 12/17/07

Previously published online as a *Human Vaccines* E-publication:
http://www.landesbioscience.com/journals/vaccines/article/5436

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Absent from both the recent and historic data is an examination of the impact smallpox vaccine has on fertility, which is important in light of the large population of reproductive-age people who receive the vaccine currently. The purpose of this study was to examine the relationship between smallpox vaccination and infertility among active-duty male and female US military service members.

Results

Of the more than 1.1 million men and women who served on continuous active duty during 2005, 395,617 were married at some point during that year, were less than 35 years of age, and served on active duty for at least 1 month in both 2003 and 2004. After excluding individuals who received any infertility diagnoses before January 1, 2005 (n = 8,451), had a live birth during the year prior to their infertility diagnosis (n = 39), had a live birth during the 9-month period immediately following their infertility diagnosis (n = 48), had a deployment of any length during 2005 (n = 85,761), and who had missing demographic data (n = 3,013), a total of 298,305 individuals remained for analysis. Forty percent of the 253,973 men in this population received the smallpox vaccine, and 28% of the 44,332 women received the smallpox vaccine.

The demographic and military-specific characteristics of the 253,973 men and 44,332 women in this analysis, by smallpox vaccination status, are displayed in Table 1. The proportion of men who received an infertility diagnosis was identical among the exposed and unexposed groups. Compared with unvaccinated males, a higher proportion of men exposed to the smallpox vaccine were younger, black, Hispanic, Army personnel, enlisted and combat or health care specialists (Table 1).

The proportion of women who received an infertility diagnosis was slightly higher among the exposed group, but this difference was not statistically significant (p = 0.103). Compared with unvaccinated women, a greater proportion of smallpox-vaccinated women were in the 25 to 29 age group, were black, Hispanic, Army, enlisted and combat specialists or in other occupations (Table 1).

Multivariable logistic regression was carried out among the male and female populations, and the results are shown in Table 2. There was no association found between receipt of an infertility diagnosis and smallpox vaccination status among men or women. However, both men and women aged 25 to 34 years were significantly more likely to receive an infertility diagnosis than were those aged 19 to 24. In addition, black non-Hispanic women were 1.30 times more likely than white non-Hispanic women to receive an infertility diagnosis [95% confidence interval (CI), 1.10–1.53]. Marine Corps men and women and Air Force women were significantly less likely to receive an infertility diagnosis than those from the other services. Finally, female health care workers were 1.23 times more likely to receive an infertility diagnosis compared with women working in all other occupations (95% CI, 1.04–1.45).

Discussion

Using military inpatient and outpatient health care utilization and vaccination data, we compared infertility diagnoses among men and women who received the smallpox vaccine with those who did not. No association was found between receipt of an infertility diagnosis and prior smallpox vaccination.

More than 1.2 million US military members have received the smallpox vaccine since December 2002 to protect against the use of smallpox as a biological weapon.[38] While adverse events associated with smallpox vaccine are well-monitored,[39,40] and the US military smallpox vaccination program has experienced low rates of adverse events,[41,42] the effect of smallpox vaccine on long-term health outcomes such as fertility remains more challenging to explore.

To date, research examining the effects of any vaccinations on male and female fertility is sparse. A 2005 study looked at the effect of anthrax vaccine on some fertility parameters among male military personnel and found no clear association between the vaccine and semen parameters.[28] While this study supports the finding that vaccination does not affect fertility, caution must be exercised when comparing anthrax vaccine with smallpox vaccine. Reported here is the first epidemiologic analysis of actual infertility diagnoses post-smallpox vaccine of which the authors are aware.

Other factors previously associated with infertility are supported by these analyses. Advanced maternal age reduces reproductive potential.[43-46] It has also been reported that higher maternal or paternal age is associated with birth defects,[47,48] miscarriages[21,49] and other pregnancy complications.[43,50,51] This investigation supports such previous work, since both men and women aged 25 years or more had significantly increased odds of receiving an infertility diagnosis. Female health care workers were also slightly more likely than those in other occupations to receive an infertility diagnosis. While one prior study reported that pregnant doctors were no more likely to receive differential obstetric treatment compared with women in other occupations,[52] the association observed in this study may have been due to increased knowledge or awareness regarding infertility among this subpopulation.

There are limitations to these analyses that should be noted. Infertility is only one of many possible manifestations of reproductive hazards, and its assessment is complex. Using electronic health care data to identify infertility is problematic and may be incomplete. Those who seek care to overcome infertility may not reflect the entire spectrum of those affected. In addition, we were unable to control for other environmental exposures that subjects may have experienced in association with receiving the smallpox vaccine. Although the large sample size of both men and women allowed for robust estimates, the total potential population was reduced by temporal restrictions and the exclusion of those who deployed in the follow-up period, in order to allow equal access to care and diagnoses in the exposed and unexposed groups. Additionally, those deployed during the follow-up period may have been healthier than those who did not deploy, and were not likely to be trying to conceive during deployment. Finally, the population was also restricted to married individuals, because without data on attempts to conceive, it is reasonable to assume that those who are married would be more likely to be trying to conceive than those who are not.

Despite limitations, these analyses offer the first large, epidemiologic investigation of infertility after smallpox vaccine. The large sample of both men and women, along with many variables to adjust for confounding, allow for a robust investigation of infertility diagnoses associated with the smallpox vaccine. The use of an objective measure of infertility, as opposed to survey-based assessments of infertility, allows for an estimate of the effect of smallpox vaccine on infertility without being influenced by recall or reporting bias.

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Table 1 **Characteristics of active-duty military men and women by smallpox vaccination exposure**

Characteristic*	Male N = 253,973				Female N = 44,332			
	Smallpox vaccinated n = 100,954		Unvaccinated n = 153,019		Smallpox vaccinated n = 12,519		Unvaccinated n = 31,813	
	n	(%)	n	(%)	n	(%)	n	(%)
Infertility status								
Reference	100,526	(99.6)	152,338	(99.6)	12,279	(98.1)	31,275	(98.3)
Infertility diagnosis	428	(0.4)	681	(0.4)	240	(1.9)	538	(1.7)
Age group, y								
19–24	25,436	(25.2)	35,979	(23.5)	4,617	(36.9)	11,865	(37.3)
25–29	42,409	(42.0)	61,825	(40.4)	5,126	(40.9)	12,365	(38.9)
30–34	33,109	(32.8)	55,215	(36.1)	2,776	(22.2)	7,583	(23.8)
Race/ethnicity								
White, non-hispanic	62,261	(61.7)	97,635	(63.8)	6,134	(49.0)	16,479	(51.8)
Black, non-hispanic	17,878	(17.7)	25,169	(16.4)	3,411	(27.3)	8,237	(25.9)
Hispanic	13,154	(13.0)	17,855	(11.7)	1,766	(14.1)	3,961	(12.4)
Other/unknown	7,661	(7.6)	12,360	(8.1)	1,208	(9.6)	3,136	(9.9)
Service branch								
Army	40,382	(40.0)	29,262	(19.1)	4,733	(37.8)	6,955	(21.9)
Navy & coast guard	23,533	(23.3)	61,144	(40.0)	2,662	(21.3)	9,588	(30.1)
Marine corps	14,744	(14.6)	22,096	(14.4)	625	(5.0)	2,293	(7.2)
Air force	22,295	(22.1)	40,517	(26.5)	4,499	(35.9)	12,977	(40.8)
Paygrade								
Enlisted	94,267	(93.4)	139,393	(91.1)	12,120	(96.8)	30,515	(95.9)
Senior enlisted & warrant officers	3,907	(3.9)	7,492	(4.9)	181	(1.4)	608	(1.9)
Commissioned officer	2,780	(2.7)	6,134	(4.0)	218	(1.7)	690	(2.2)
Military occupation								
All others	71,250	(70.6)	123,021	(80.4)	9,312	(74.4)	23,593	(74.2)
Combat specialists	23,623	(23.4)	21,120	(13.8)	823	(6.6)	1,601	(5.0)
Health care	6,081	(6.0)	8,878	(5.8)	2,384	(19.0)	6,619	(20.8)

*All chi-square tests of significance except infertility status were statistically significant at $p < 0.05$.

In summary, this study found no association between infertility diagnoses after receiving smallpox vaccination. These results may be reassuring to vaccine recipients and public health professionals. Future studies should continue to explore the full spectrum of reproductive health challenges after exposures of concern.

Methods

Data. Smallpox immunization status was obtained from records from the Defense Enrollment Eligibility Reporting System at the Defense Manpower Data Center in Monterey Bay, CA. Demographic and military-specific data were obtained from military records. Infertility data were obtained from the Standard Inpatient Data Record, the Health Care Service Record, and the Standard Ambulatory Data Record, representing all care to active-duty members, inpatient and outpatient, at military and civilian facilities. Infertility diagnoses were identified using *International Classification of Diseases*, Ninth Revision, Clinical Modifications (ICD-9-CM) codes. The Department of Defense Birth and Infant Health Registry was used to identify subjects with live births on record for the purposes of determining primary and secondary infertility. Files were obtained in electronic format and were linked using personal identifiers.

Study population and outcomes. This retrospective cohort study included military personnel who served on continuous active duty during 2005, were less than 35 years of age throughout 2005, were married in 2005, and served on active duty for at least one month in both 2003 and 2004. The population was stratified by gender, and exposure and outcome groups were determined. The exposure of interest in this study was smallpox vaccine, and those who received a smallpox vaccine in the calendar year 2003 or 2004 were considered exposed. Those who never received a smallpox vaccine or received a vaccine in 2005 or 2006, after the defined exposure window, were considered not exposed. Infertility, the outcome for this study, was then assessed at least one year after the date of vaccination. Men and women who received an infertility diagnosis any time during 2005 were considered cases, and must have been vaccinated at least one year prior to receipt of the infertility diagnosis. Infertility was assessed using the ICD-9-CM codes 606.x for men and 628.x for women. Primary infertility was defined as receipt of an infertility diagnosis without any previous

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Table 2 **Adjusted odds of receiving an infertility diagnosis in 2005 among active-duty military personnel by smallpox vaccination status**

Characteristic	Male N = 253,973		Female N = 44,332	
	OR*	95% CI*	OR*	95% CI*
Smallpox vaccination status				
Unvaccinated	1.00	—	1.00	—
Vaccinated†	0.94	(0.83, 1.06)	1.10	(0.94, 1.28)
Age group, y				
19–24	1.00	—	1.00	—
25–29	**1.73**	**(1.45, 2.06)**	**1.37**	**(1.15, 1.62)**
30–34	**1.83**	**(1.52, 2.20)**	**1.35**	**(1.11, 1.64)**
Race/ethnicity				
White, non-Hispanic	1.00	—	1.00	—
Black, non-Hispanic	1.16	(0.99, 1.35)	**1.30**	**(1.10, 1.53)**
Hispanic	1.02	(0.85, 1.23)	1.03	(0.82, 1.30)
Other/unknown	0.81	(0.63, 1.03)	0.84	(0.64, 1.11)
Service branch				
Army	1.00	—	1.00	—
Navy & Coast Guard	0.89	(0.76, 1.03)	0.90	(0.75, 1.09)
Marine Corps	**0.76**	**(0.61, 0.94)**	**0.40**	**(0.26, 0.63)**
Air Force	0.91	(0.77, 1.07)	**0.78**	**(0.65, 0.93)**
Paygrade				
Enlisted	1.00	—	1.00	—
Senior enlisted & warrant officers	0.93	(0.70, 1.24)	0.75	(0.42, 1.35)
Commissioned officer	0.95	(0.68, 1.33)	1.36	(0.85, 2.17)
Military occupation				
All others	1.00	—	1.00	—
Combat specialists	0.94	(0.80, 1.11)	0.68	(0.46, 1.00)
Health care	0.98	(0.77, 1.26)	**1.23**	**(1.04, 1.45)**

*Odds ratios and associated 95% confidence intervals are adjusted for all other variables in the table. †Military personnel in the vaccinated group received the smallpox vaccine in 2003 or 2004.

live births on record. Secondary infertility was defined as receipt of an infertility diagnosis with at least one live birth on record greater than 1 year prior to the infertility diagnosis date. Individuals were excluded from the study if they received any infertility diagnoses before January 1, 2005, had a live birth during the year prior to their infertility diagnosis, had a live birth during the 9-month period immediately following their infertility diagnosis, had a deployment of any length during 2005 (since deployment would limit accessibility to the health care system for infertility diagnoses), or had missing demographic data.

Statistical analyses. Pearson chi-square tests were used to examine the unadjusted measures of association between infertility and smallpox vaccination status, demographic and military-specific characteristics. Collinearity among the independent variables was assessed using regression diagnostics, and variables were tested as possible confounders. Logistic regression was used to compare the odds of receipt of an infertility diagnosis among the group exposed to smallpox vaccine with the odds of receipt of an infertility diagnosis among the unexposed group, while simultaneously adjusting for all other variables in the model. Parallel analyses were conducted for the male and female population. All analyses were carried out using SAS software (version 9.1.3, SAS Institute, Inc., Cary, NC).

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Acknowledgements

We thank Scott L. Seggerman and Greg D. Boyd from the Defense Manpower Data Center, Monterey Bay, California, for providing the demographic and deployment data. We thank Michelle Stoia, from the Naval Health Research Center, San Diego, California, for editorial assistance. We appreciate the support of the Henry M. Jackson Foundation for the Advancement of Military Medicine, Rockville, Maryland.

This represents report 07-27, supported by the Department of Defense, under work unit no. 60504. The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of the Army, Department of the Air Force, Department of Defense, or the US Government. This research has been conducted in compliance with all applicable federal regulations governing the protection of human subjects in research (Protocol NHRC.2003.0018).

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1. Report Date (DD MM YY)
27/07/07

2. Report Type
New

3. DATES COVERED (from - to)
2003-2005

4. TITLE AND SUBTITLE
Smallpox Vaccination Is Not Associated With Infertility in a Healthy Young Adult Population

5a. Contract Number:
5b. Grant Number:
5c. Program Element:
5d. Project Number:
5e. Task Number:
5f. Work Unit Number: 60504

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9. PERFORMING ORGANIZATION REPORT NUMBER
Report No. 07-27

10. Sponsor/Monitor's Acronyms(s)
NMRC/NMSC

11. Sponsor/Monitor's Report Number(s)

12 DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution is unlimited.

13. SUPPLEMENTARY NOTES

14. ABSTRACT (maximum 200 words)

OBJECTIVE: To evaluate infertility diagnoses in a large population of healthy young adults in relation to prior smallpox vaccination.

STUDY DESIGN: Retrospective cohort of United States military members eligible for smallpox vaccination in 2003-2004 and with electronic health care utilization records available through at least December 2005. Multivariable logistic regression models were applied to evaluate infertility among male and female populations separately.

RESULTS: Among 253,973 men and 44,332 women included in the analyses, the adjusted odds of infertility diagnoses in those with prior smallpox vaccination were 0.94 (95% CI, 0.83-1.06) and 1.10 (95% CI, 0.94-1.28), respectively. This study had ample power to detect whether individuals receiving the smallpox vaccine were more or less likely to receive an infertility diagnosis.

CONCLUSION: Smallpox vaccination was not associated with subsequent infertility diagnoses in either men or women.

15. SUBJECT TERMS
infertility, smallpox vaccine, military personnel, reproductive health, immunization, vaccination

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b.ABSTRACT	b. THIS PAGE			Commanding Officer
UNCL	UNCL	UNCL	UNCL	5	19b. TELEPHONE NUMBER (INCLUDING AREA CODE) COMM/DSN: (619) 553-8429